Critical Care

CORRESPONDENCE

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How to define parenteral nutrition

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In the context of an international, multicentre observational study—the GUTPHOS study [1]—the investigators documented the use of parenteral nutrition (PN), including daily energy intake via this route. A secondary outcome, "days free of PN," was planned to validate a gastrointestinal dysfunction score. During data quality check, we observed that the definition of PN varied among the participating sites. This observation was further confirmed in a subsequent survey, in which the sites were asked to report the approach they used to document PN. All 28 GUTPHOS study sites (21 from Europe, four from Asia, one from North America, one from South America and one from Oceania) responded and reported their approach (Fig. 1A). In addition to some expectable differences in practice (e.g., using multi-chamber bags vs. separate components), relevant conceptual variability was observed, leading the steering committee to develop a consensus definition for PN in GUTPHOS: "The administration of intravenous amino acids or lipids alone, or any combination of at least two macronutrient components is considered as being PN, whereas administration of only glucose in any concentration is not." Sites adjusted their data accordingly.

In this correspondence, we aim to draw attention to the unclear definition of PN and call for action.

Despite numerous guidelines and studies addressing PN in the literature, clear guidance on which components and amounts are necessary to define PN for clinical studies still needs to be provided. The European Society for Clinical Nutrition and Metabolism (ESPEN) defines PN as a nutrition therapy provided through intravenous (central or peripheral) administration of amino acids, glucose, lipids, electrolytes, vitamins and trace elements [2]. The American Society for Parenteral and Enteral Nutrition (ASPEN) defines PN as nutrition provided when patients cannot use the gastrointestinal (GI) tract or nutrition needs cannot be met through the GI tract alone [3]. ESPEN guidelines on ICU nutrition mention that parenteral and enteral feeding preparations differ because commercially available PN solutions contain amino acids and glucose with or without lipids (multi-chamber bags) but no micronutrients for stability reasons [4]. While it is clear that providing all macronutrients and micronutrients intravenously is considered PN, the minimum requirements for defining PN in clinical studies need to be clarified (Fig. 1B).

When PN was first introduced in the 1960s, it was initially called "total parenteral nutrition (TPN)", designed to cover all nutrition needs, i.e. to provide fluid, protein, carbohydrate, fat, vitamins, trace elements and minerals. The term was simplified to PN after the start of the millennium, and this abbreviation has led to different interpretations. Our current observation suggests the need to define PN more precisely for clinical studies. In the ongoing GUTPHOS study, the question of the PN definition was never raised during the study protocol development nor by sites during data collection, although the Case Report Form manual listed dextrose-based maintenance solutions as non-nutritional calories, yet without further specification and guidance. Our observation suggests a high confidence level in personal or local interpretations,

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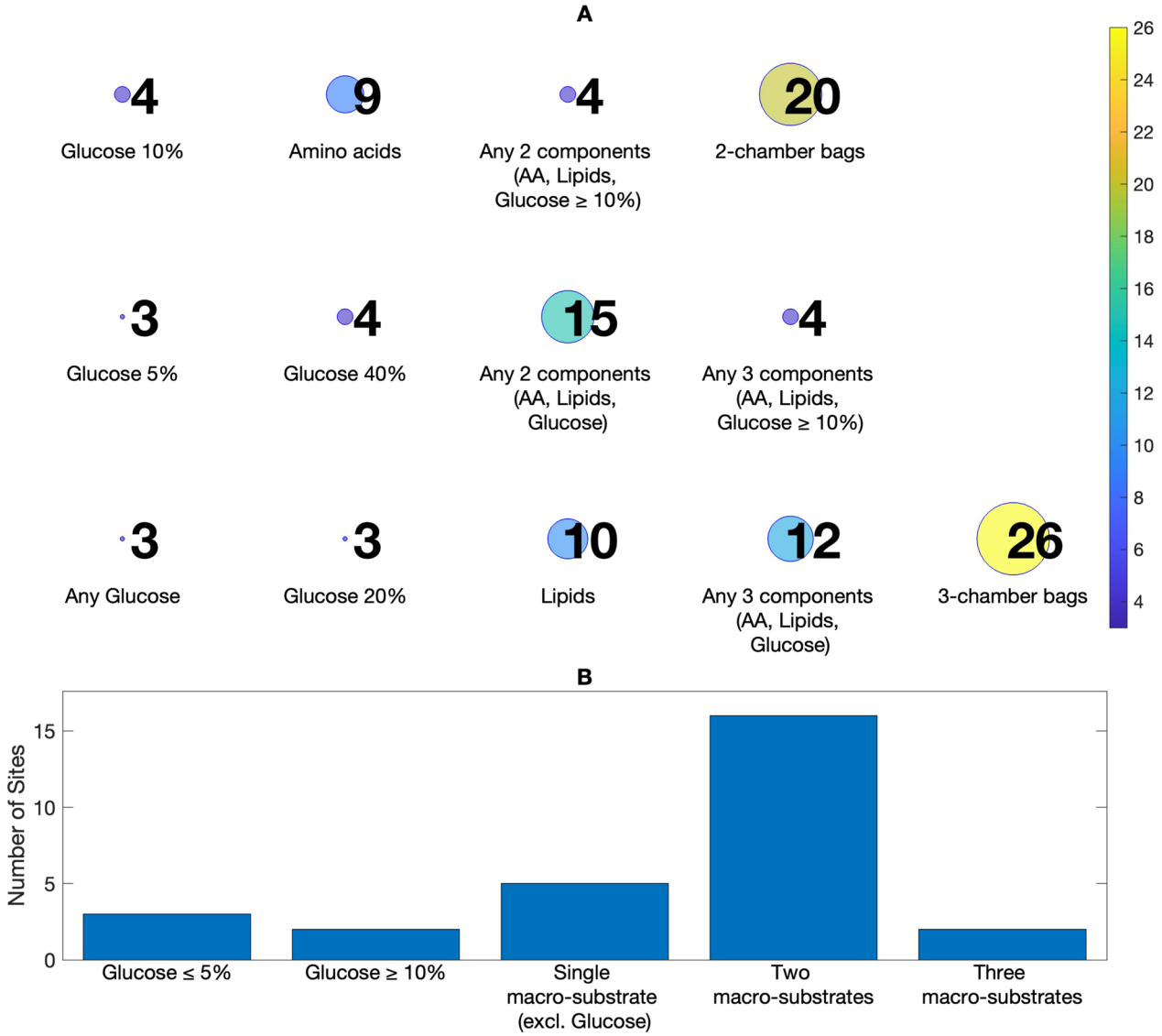

Fig. 1 Results of the survey among 28 sites participating in the GUTPHOS study. **A** Frequency of Positive Responses for PN Options. Bubble chart representing the frequency of responses for different Parenteral Nutrition (PN) options in the survey with 28 sites. Each bubble represents a PN option. Each bubble's size and colour intensity correspond to the number of positive responses for that option, with larger and brighter bubbles indicating more frequent selection. The number inside each bubble indicates the exact count of positive responses. PN options are labelled beneath each bubble. *AA* amino acids. **B** Summary of minimum requirements to label a solution as PN. Bar chart illustrating the diversity in defining Parenteral Nutrition (PN) among survey respondents. The x-axis shows five categories of increasing complexity in PN definition, from "Any single component" to "Only commercial preparations." The y-axis and bar heights represent the number of responses in each category. The sites were categorised according to the minimal definition (left-to-right on the x-axis)

whereas, in reality, these interpretations are widely different. In randomised controlled trials (RCT) investigating specific PN products, the variation in definition may be less important than in observational studies. The most recent large NUTRIREA-3 RCT defined PN as "ternary admixture bags containing three groups of macronutrients used according to standard practice" [5]. However, in the NUTRIREA-2 and CALORIES RCTs that compared enteral nutrition (EN) vs. PN, PN was defined as nutrition provided through a central venous catheter [6, 7], leaving considerable space for different interpretations. Accordingly, RCTs would benefit from a detailed definition of PN.

Developing a precise PN definition is challenging. On the one hand, any substrate (glucose, amino acid, lipid) delivered intravenously, independent of the amount

and indication, are parenteral nutrients that could be considered PN. On the other hand, from the perspective of sustaining life over an extended period of time, PN would be defined as covering the body's requirement for all macro- and micro-nutrients. Therefore, another relevant question arises: Should supplemental PN (SPN), used in conjunction with oral or enteral intake, be defined differently regarding its composition? With such differentiation, PN administered together with EN is not always considered SPN when capturing different feeding routes in studies or databases.

Taken together, despite a simple initial definition of PN that seemed intuitively clear to most clinicians, a precise, unified definition for data comparison in clinical studies is not available and needs to be developed. The above definition, retrospectively applied to the GUTPHOS study, should only be understood as a compromise aiming at unifying results from different sites in a particular study rather than a consensus definition proposal. We wish to draw attention to varying interpretations of "PN" as a pitfall hindering comparisons between sites or studies. We call critical care and nutrition societies for a joint effort to find a global consensus on a detailed definition of PN.

Abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
EN	Enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
ICU	Intensive care unit
PN	Parenteral nutrition
RCT	Randomized controlled trial

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Author contributions
ARB, AC, MMB, MP and KFB conceptualised and drafted the manuscript, KFB visualised the results, and all the co-authors reviewed and revised the manuscript.

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Availability of data and materials
Data will be made available on reasonable request.

Declarations

Ethics approval and consent to participate
The GUTPHOS study was primarily approved by the University of Tartu Ethics Committee on May 29th, 2023 (approval number 377/T-15), and each participating site obtained local ethics committee approval according to local site country and institutional regulations.

Consent for publication
Not applicable.

Competing interests
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References

1. Kouw IWK, Melchers M, Mändul M, Arabi YM, Casaer MP, Cotoia A, et al. Prospective multicenter study to validate the gastrointestinal dysfunction score (GIDS) in intensive care patients: study protocol for Part A of the international GUTPHOS study. Clin Nutr ESPEN. 2024;63:702–8.
2. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49–64.
3. American Society for Parenteral and Enteral Nutrition website: https://www.nutritioncare.org/About_Clinical_Nutrition/What_Is_Parenteral_Nutrition_/#:~:text=Parenteral%20nutrition%20(Parenteral%20%5Bpah%20REN,through%20the%20GI%20tract%20alone.
4. Singer P, Reintam Blaser A, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48–79.
5. Reignier J, Plantefeve G, Mira JP, Argaud L, Asfar P, Aissaoui N, et al. Low versus standard calorie and protein feeding in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3). Lancet Respir Med. 2023;11(7):602–12.
6. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133–43.
7. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673–84.

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